Recent Advances and Future Directions in Cancer Nanotechnology

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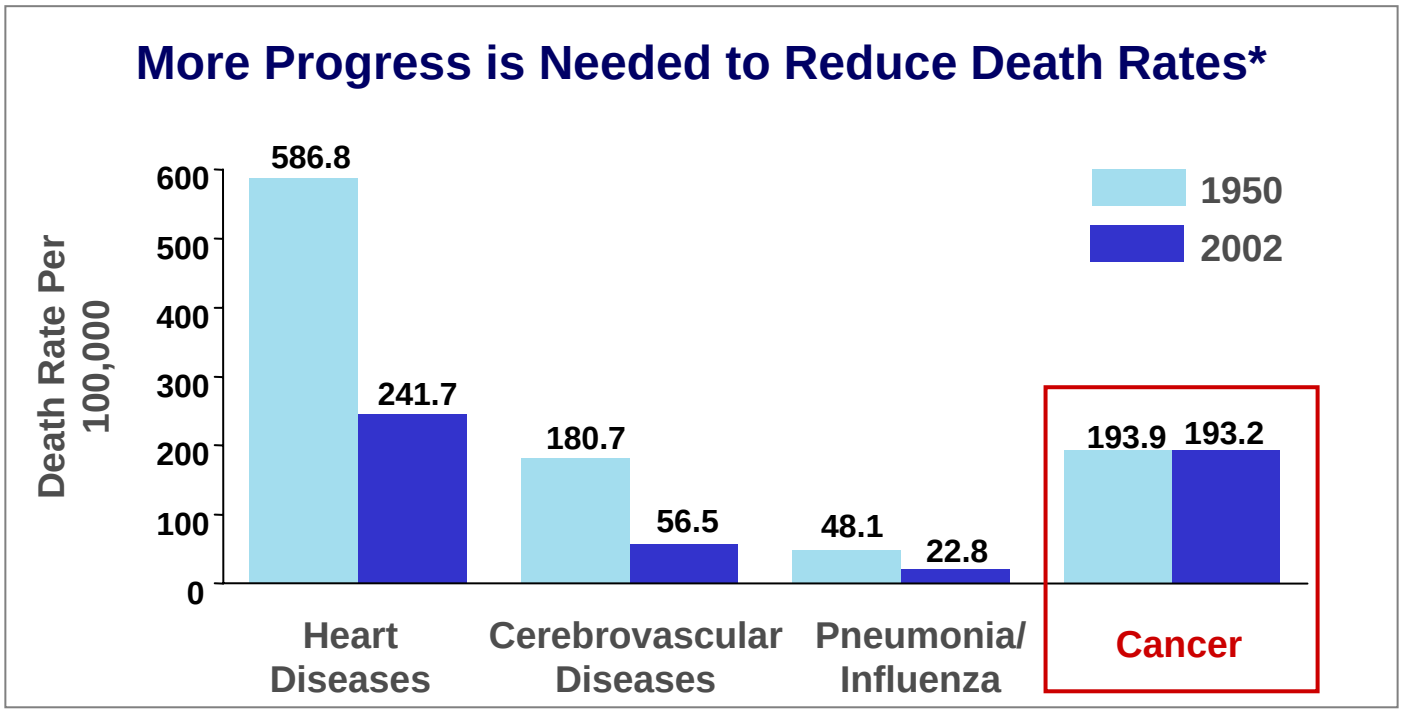
Cancer's Burden

- 556,900 Americans will die of cancer this year
- 1,372,900 Americans will hear the words "you have cancer…" this year



Molecular Medicine Is Transforming Discovery/Development/Delivery

MOLECULAR MEDICINE

Beating cancer

Oct 14th 2004
From The Economist print edition

The war on cancer is entering a new phase

"CANCER" is one of those words that sends shivers down the spine. The phrase "battle with cancer" is a headline writer's cliché. And the military metaphor was widened in 1971, when Richard Nixon, then president of the United States, announced an initiative that later became known as the "war on cancer". Cancer, however, has not been beaten. Indeed, by some measures the problem is worse than it was three decades ago. It is true that treatments have improved somewhat, and prognoses with them, and that a few forms of the disease, particularly in children, can be cleared up altogether. But the biggest success has been due to people giving up smoking, rather than to new treatments. And despite that success, the likelihood that a person will get cancer at some point in his life has actually risen since Nixon's speech.

the past three decades of effort have seemed a disappointment, the next ecade could prove to be one of rapid progress. The battle against cancer is at a rning-point. Because of recent advances, it is becoming possible to imagine a e in the not-too-distant future when new medical treatments will be able to ne the disease, transforming it from a potent killer into something akin to a onic complaint. The day when cancer no longer strikes terror in the heart of se diagnosed with it may not be far away (see article).

earchers have unravelled much of the basic molecular biology of cancer and, ed by the outpouring of knowledge that the Human Genome Project has fed over the past ten years, they have come to understand how the disease esses. Indeed, they have come to understand far more clearly than before the term "cancer" properly refers not to a single disease but rather to a whole of diseases that have in common only the fact that they are caused by cells o not know when to stop dividing. That understanding has now reached the where it can be turned into action. The next few years should see an array of reatments that will add up to a big change in the way that cancer is viewed alt with by society.

Molecular Medicine Is Already in Practice

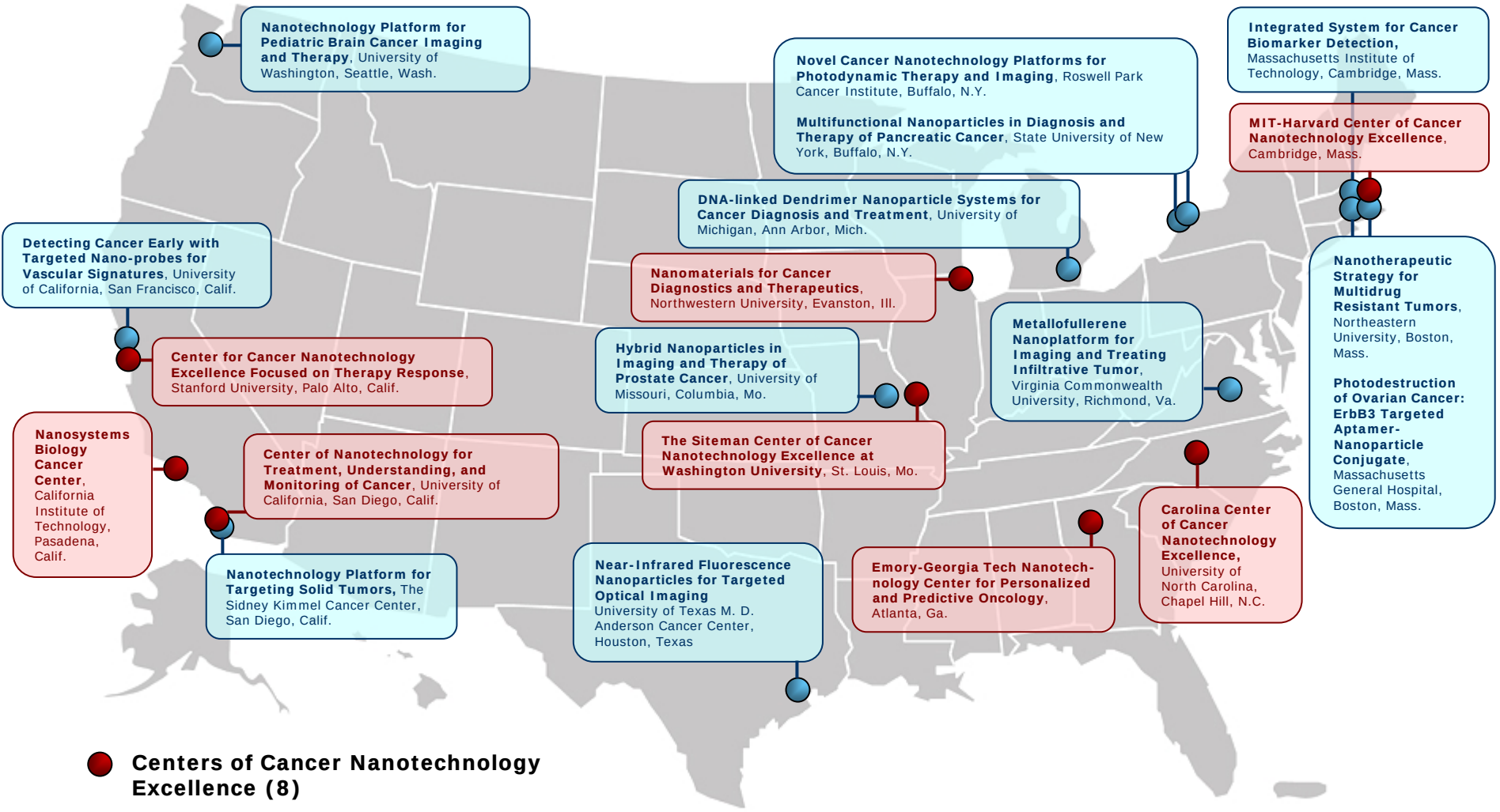
- Breast cancer:
  - HercepTest detects HER2 to identify 20-30% responders to Herceptin
  - Oncotype Dx detects 21 gene profile to guide chemotherapy strategies in individuals with low (47%), intermediate (32%) and high risk (21%) of recurrence
  - BRCA1/2 test identifies ~1/500 women with mutation associated with high risk of breast cancer, triggering frequent surveillance or preventive treatments
- Colorectal cancer: UGT1A test guides dosage adjustment for 10% of individuals likely to experience toxicity from Camptostar (irinotecan)
- Acute lymphoblastic leukemia: TPMT test guides dosage adjustment for 1/300 individuals likely to experience toxicity from Purinethol (mercaptopurine)
- Melanoma: p16 test identifies 44% of individuals with high risk mutation in melanoma-prone families, triggering frequent disease surveillance

Nanotechnology

- **The Opportunity:**
  - Multifunctional structures that can target cancer processes at the subcellular level

- **NCI Approach:**
  - Investments since 1998 in novel technologies through Unconventional Innovations Program
  - Development of Cancer Nanotechnology Plan
  - Launch in 2004 of NCI Alliance for Nanotechnology in Cancer with $144.3 million commitment, designed to “ignite” nano-product development and commercialization

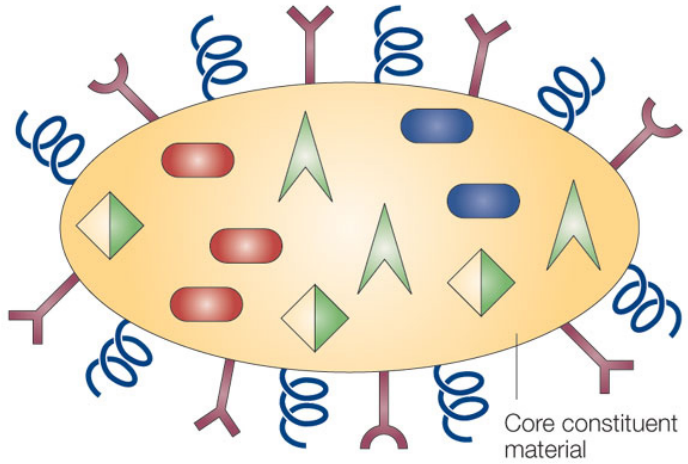
Alliance Program Awards



Nanotech Will Enable Targeted Therapies

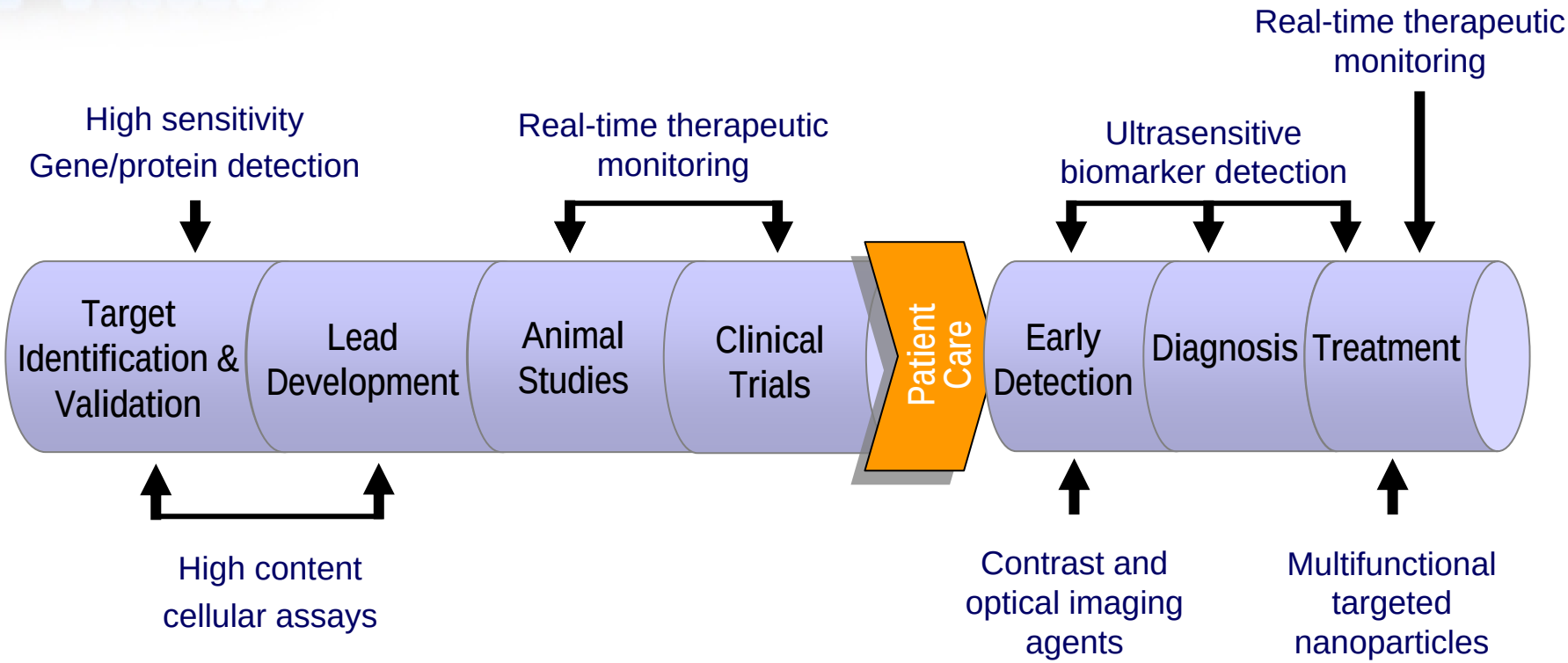
- Problem:
- Current treatments - severe side effects
- Current treatments kill healthy cells
- Maintaining effective dose in circulation is difficult
- Multi-drug resistance often occurs

- Solution:
- Treatments for controlled and sustained delivery
- Drug-delivery systems that combine targeting agents with efficacy reporters
- Tumor-specific “heat-kill” or “light-kill” treatments



M. Ferrari, Nature Reviews, March 2005

Detection, Treatment, Prevention: Bench to Bedside



Real-Time Detection of Individual Biomolecules in a Flow Channel

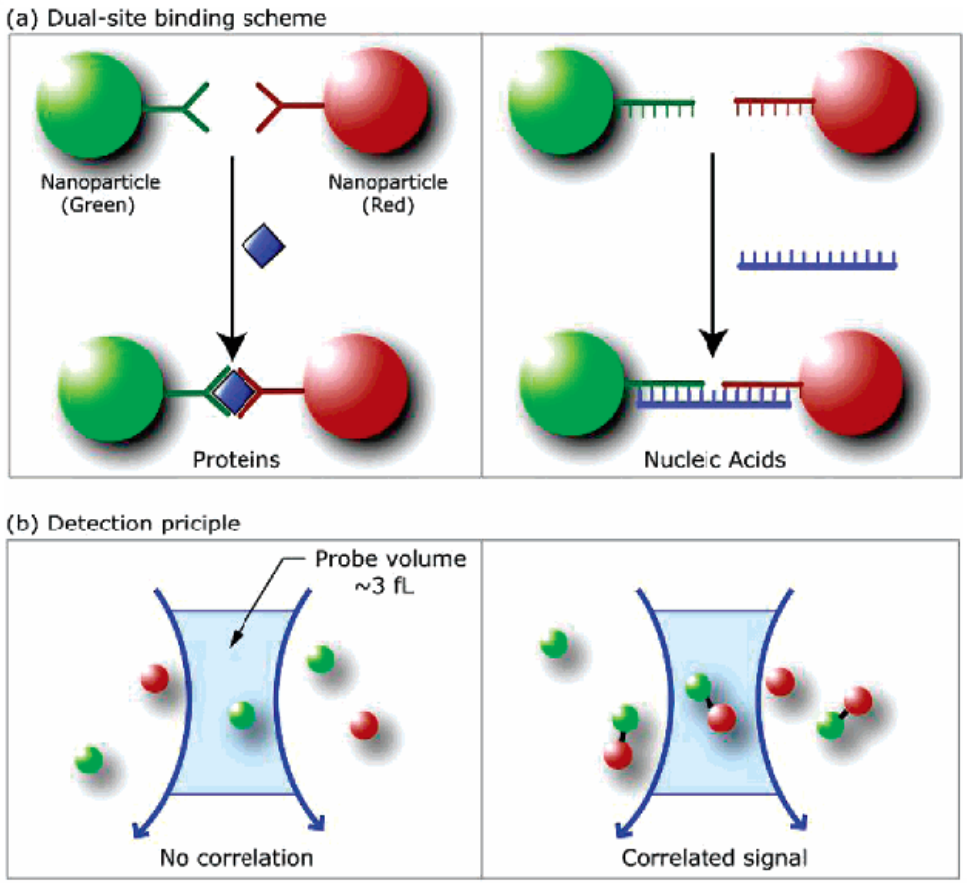
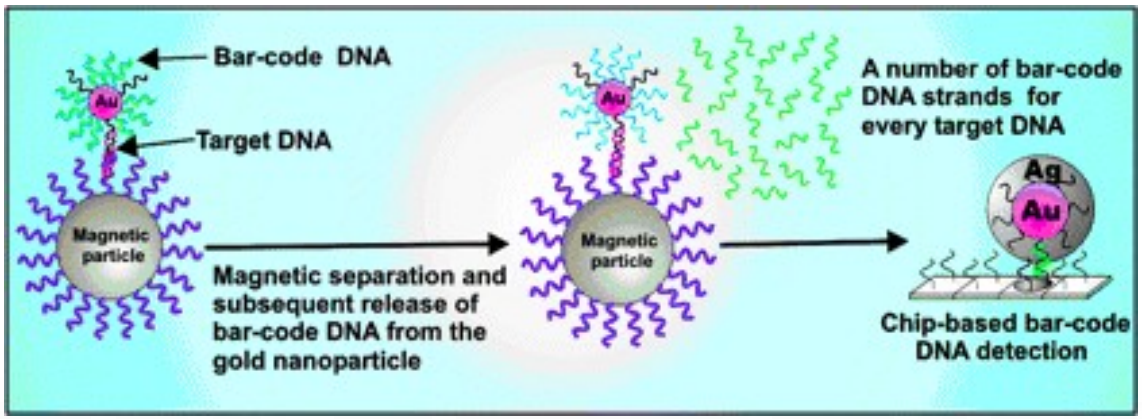
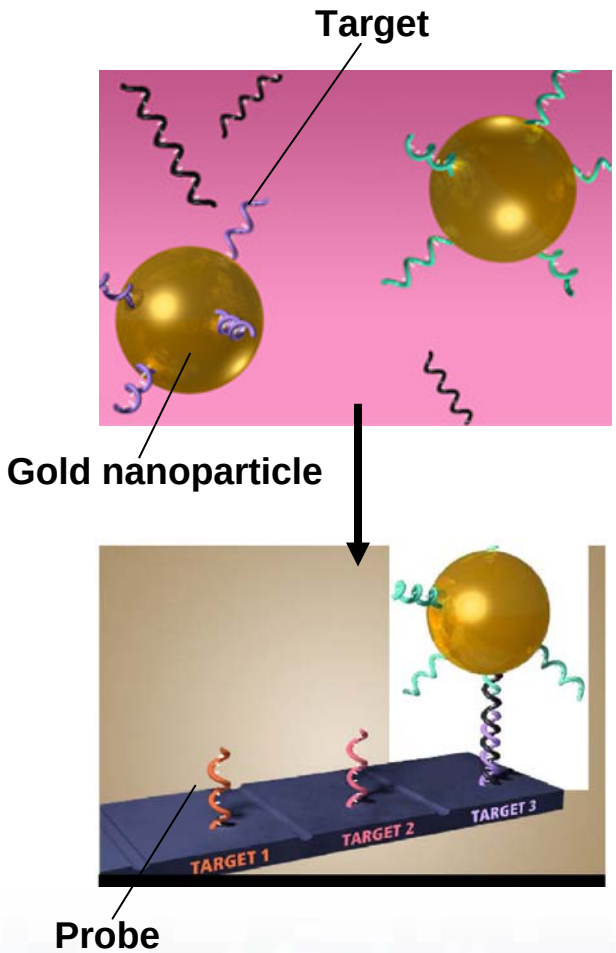


Image courtesy of Shuming Nie, Ph.D
A. Agrawal et al., *Analytical Chemistry*, 2006

Early Detection
Nanoparticle-based Detection

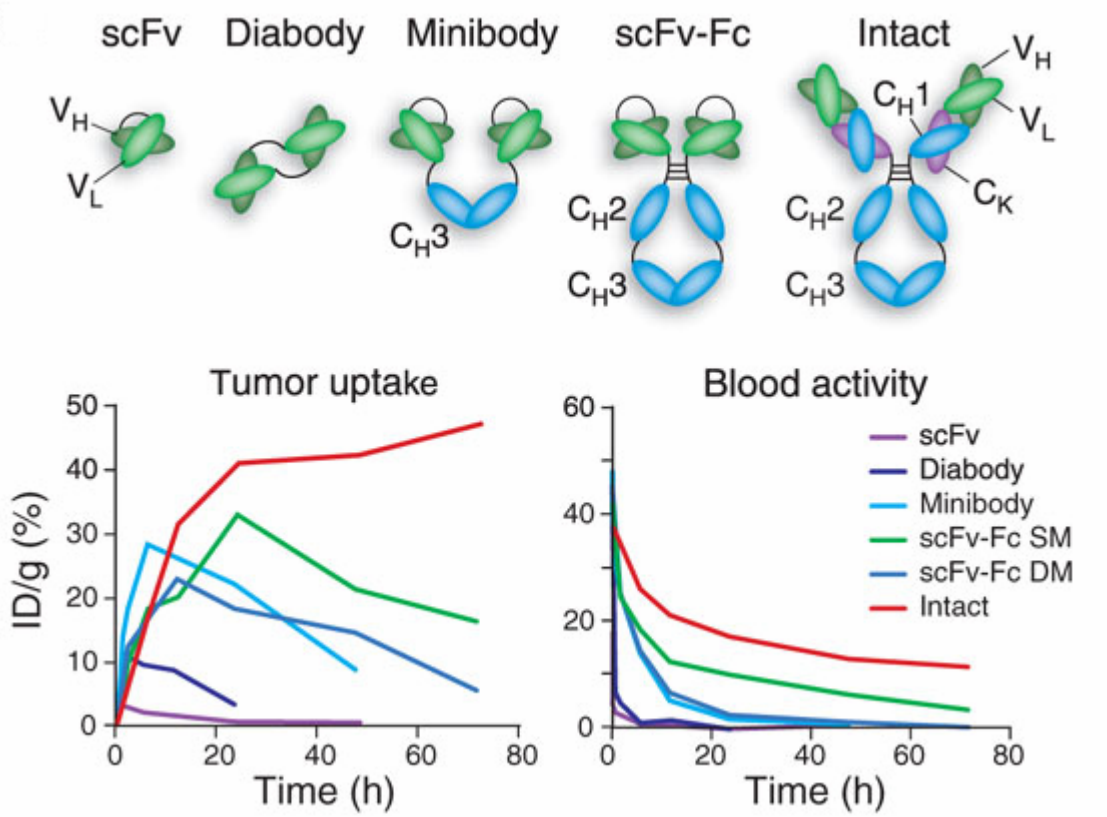
- Developing platforms with high specificity, sensitivity, reproducibility (better than ELISA)
- Nanoparticles enable detection sensitivity for proteins equivalent to PCR for nucleic acids





Source: Nam, Mirkin et al. JACS *126*, 5932 (2004)

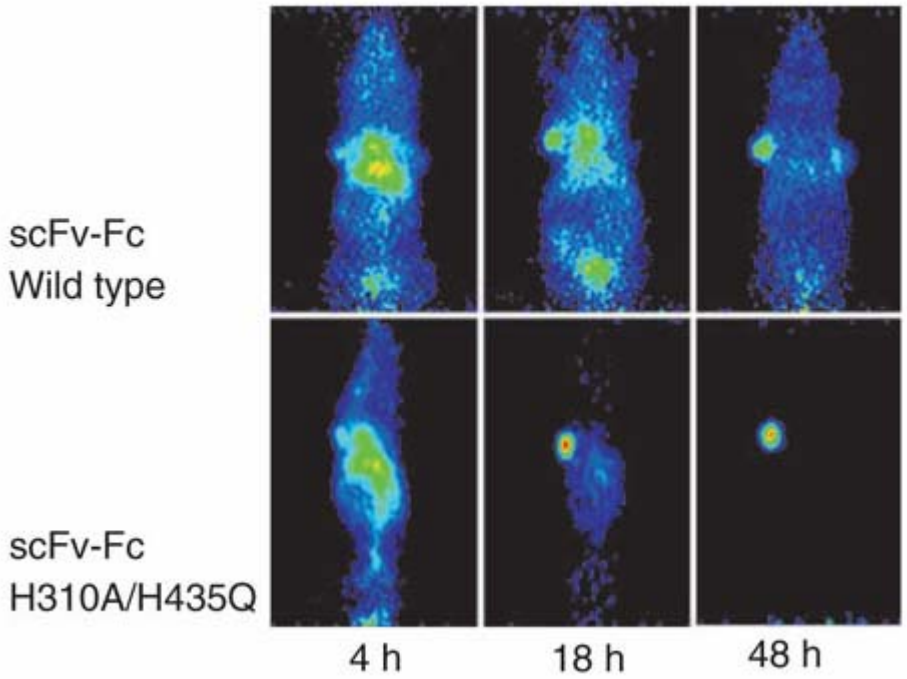
Targeting with Engineered Antibody Fragments



Wu and Senter, Nature Biotech. Volume 23, number 9, September, 2005.

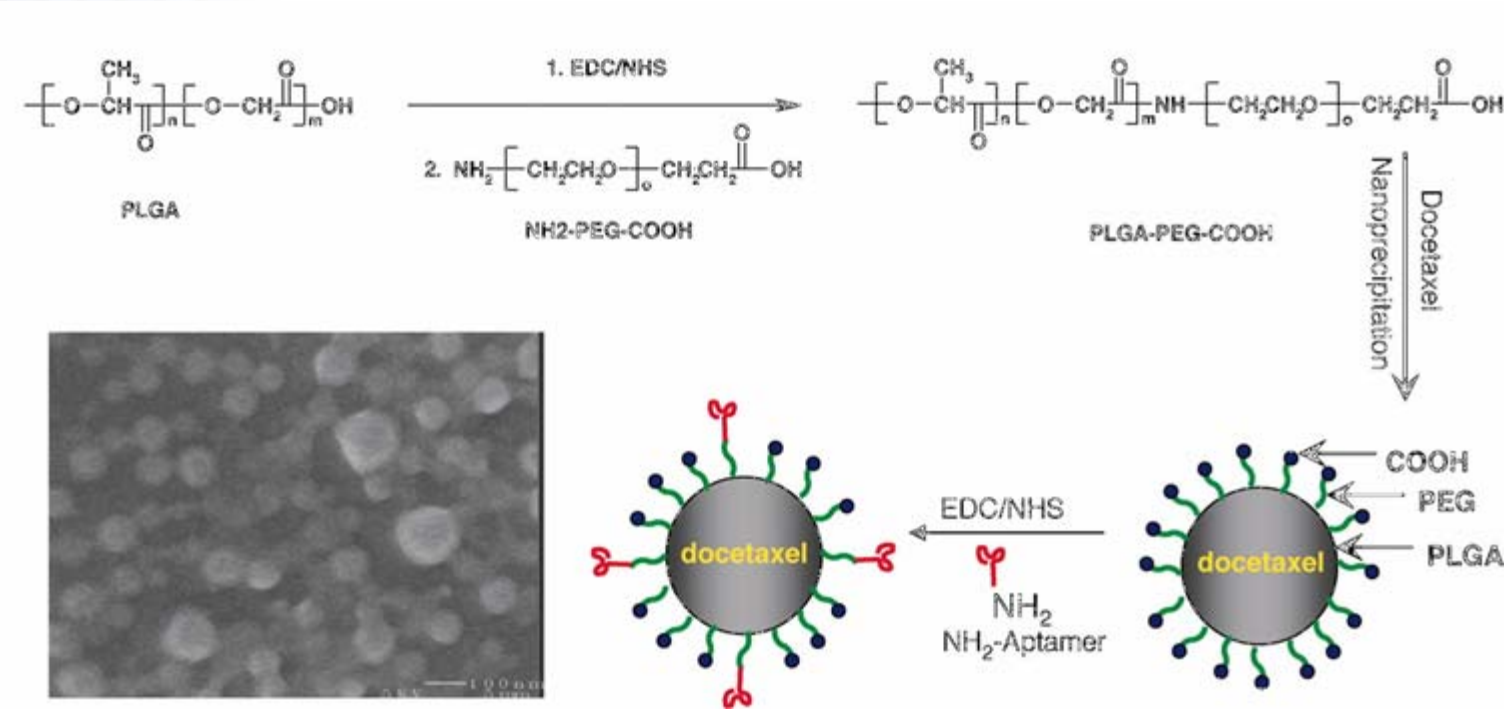
Serial microPET Imaging of ^{124}I-labeled Antibody Fragments- Effect of Mutations

→ Ability to measure level of antigen in vivo



Next steps: beyond radiolabelling- QDs, magnetic NPs, liposomes, etc.

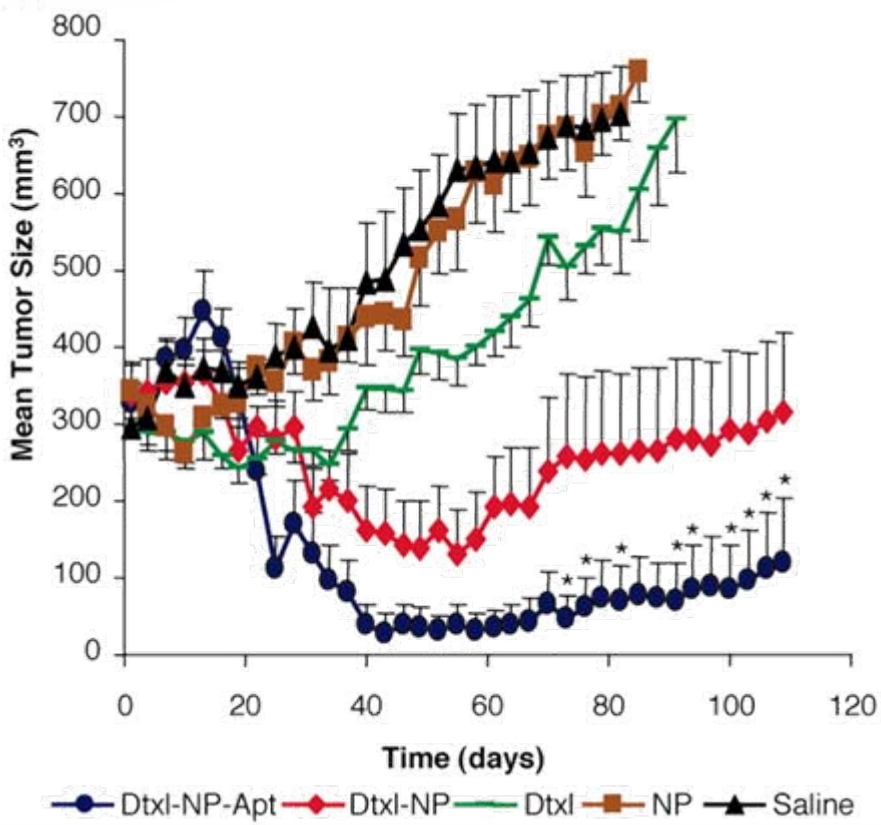
Docetaxel-Encapsulated Pegylated PLGA Nanoparticle-Aptamer Conjugates

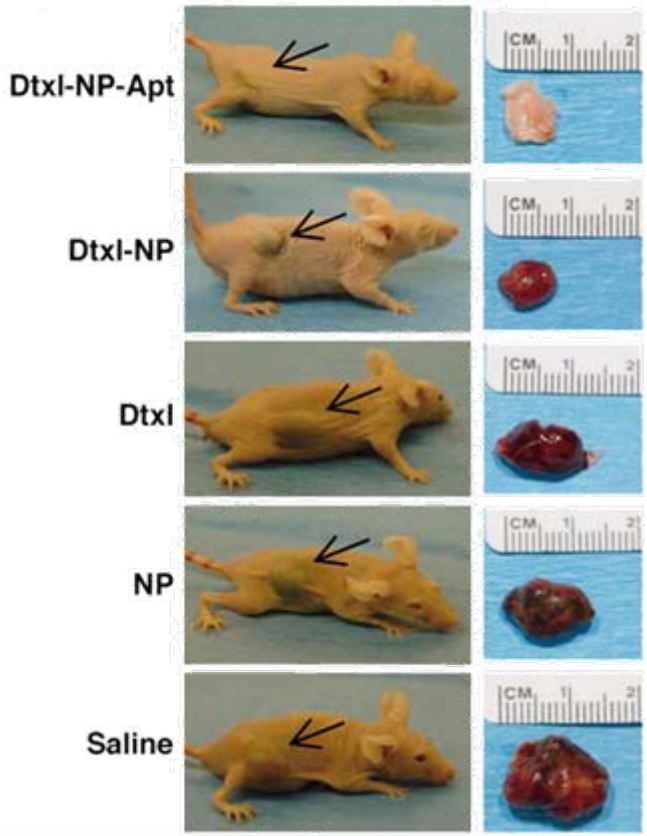


Aptamers are DNA or RNA oligonucleotides that bind to antigen with high affinity and specificity

Farokhzad et al. PNAS, April 18, 2006, vol. 103, no.16, 6315-6320.

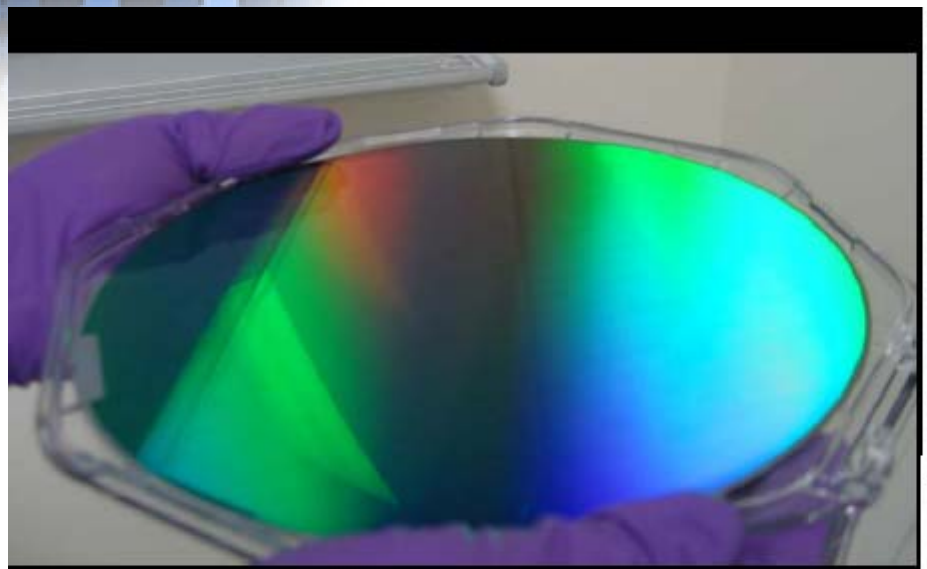
Comparative Efficacy Study



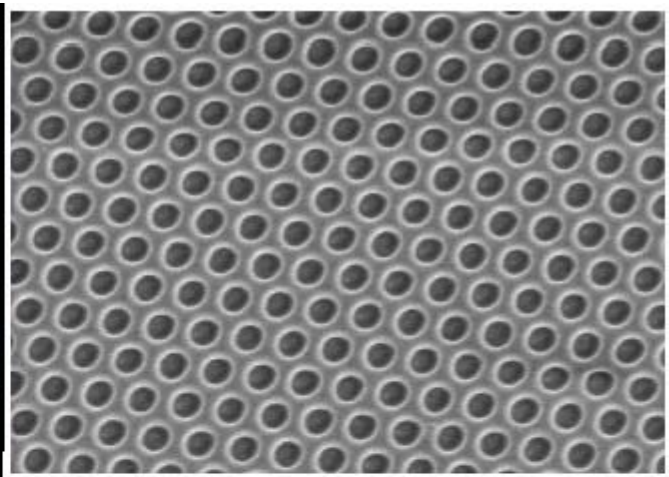


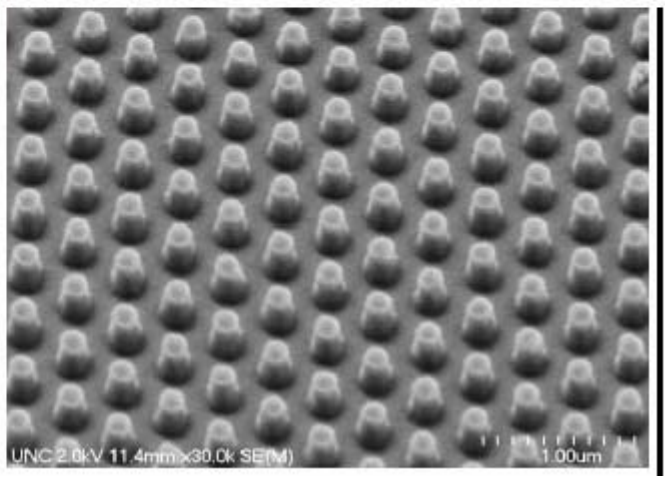
LNCaP s.c. xenograft nude mouse model of PCa; single intratumoral injection (day 0)

Organic Nanoparticles via PRINT (Particle Replication in Nonwetting Templates)



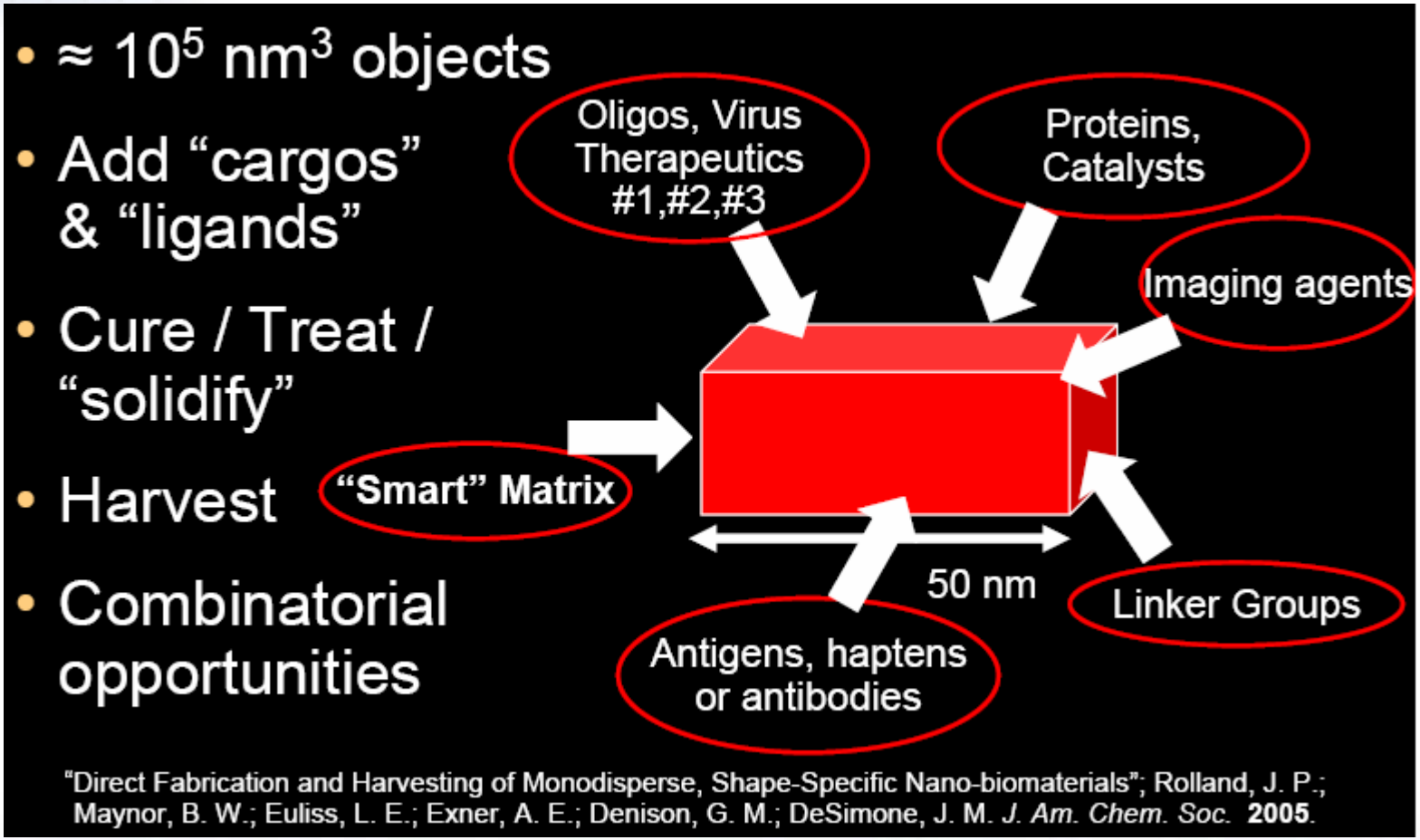
- 8 inch wafer, canonical posts, each post is 160 nm at top tapered to 200 nm at bottom to facilitate harvesting;
- Generates 8 mgs / wafer
- Micrographs show nanoparticles on medical adhesive harvesting layer at 45° angle



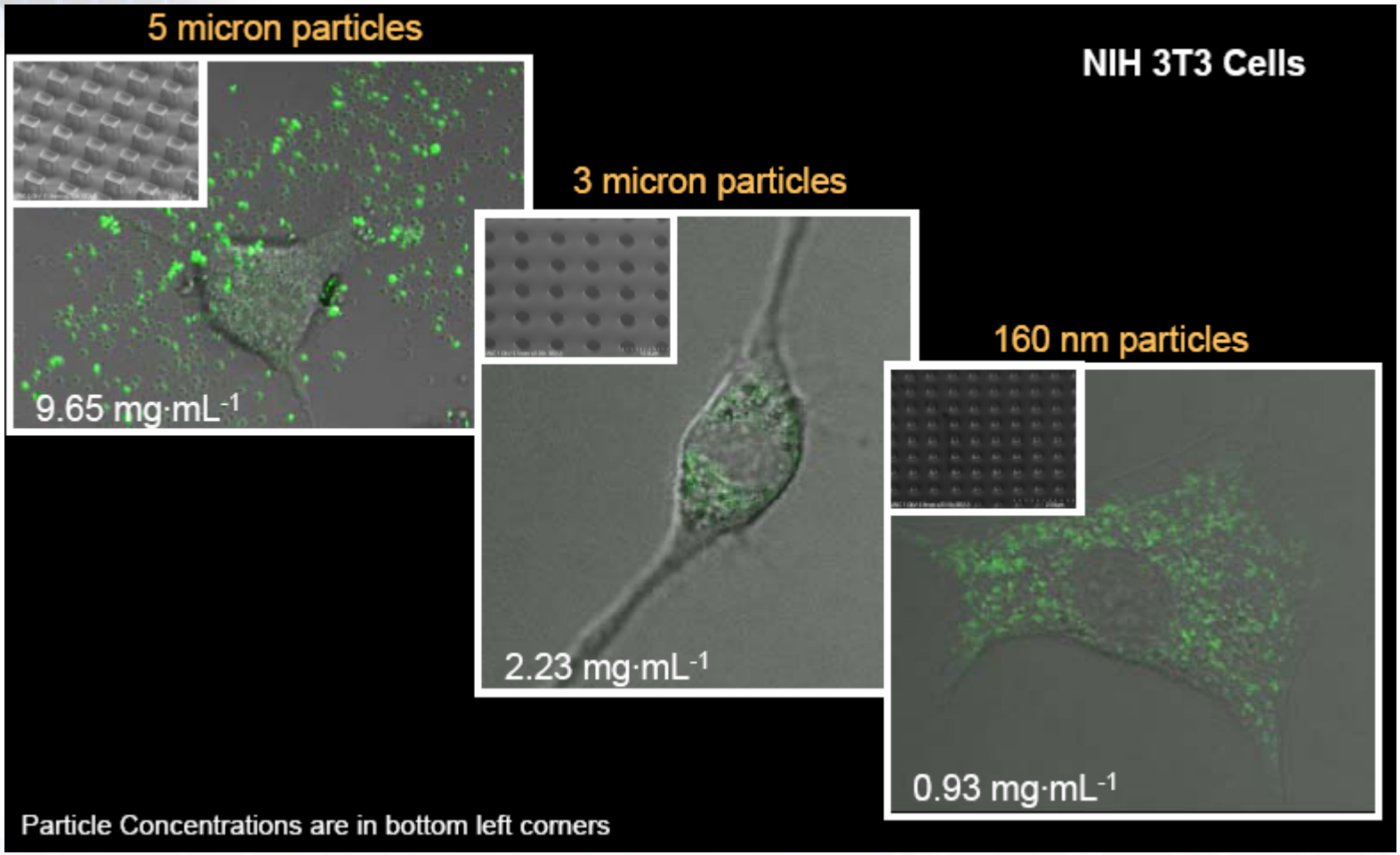


Non-wetting substrate and PFPE mold enable gentle fabrication of organic materials; rigorous control of shape, size, and chemical structure

“Smart Particles” for Nanomedicine by Adapting Emerging Technologies from the Semiconductor Industry

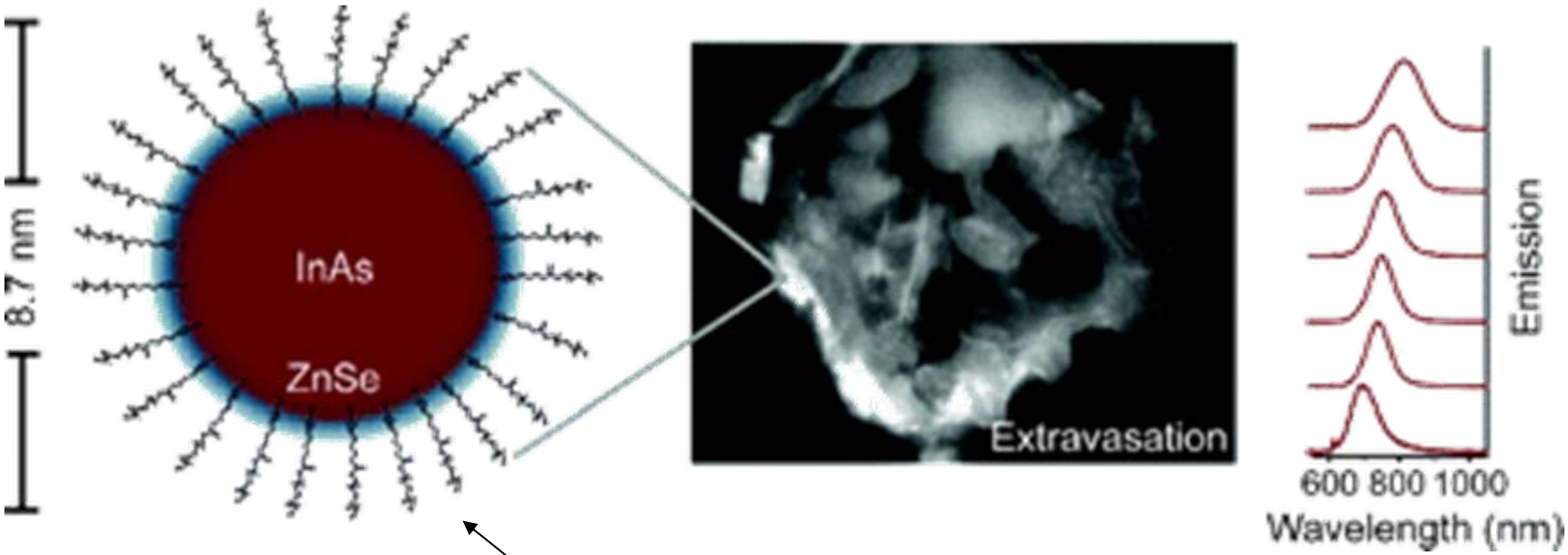


Size Effects on Particle Uptake



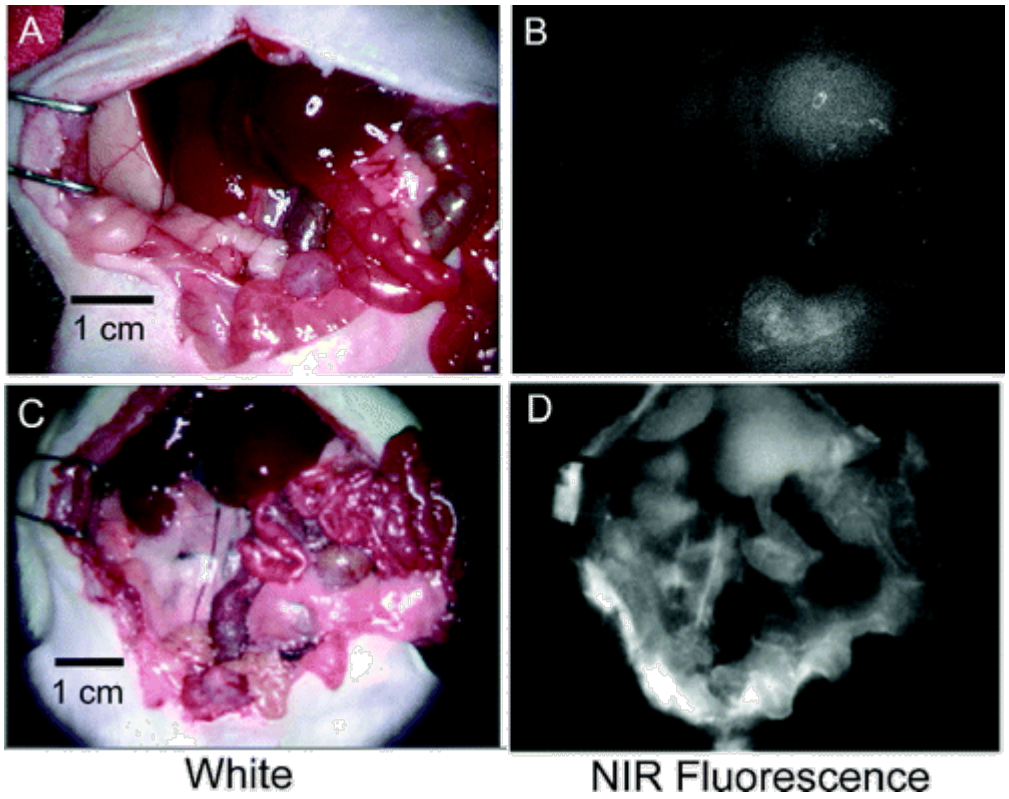
Small Indium Arsenide-Zinc Selenide Core-Shell Nanocrystals

(InAs)ZnSe (core)shell QDs emit in NIR and exhibit HD < 10 nm



Zimmer, Bawendi et al. JACS, 2006, 128, 2526-2527

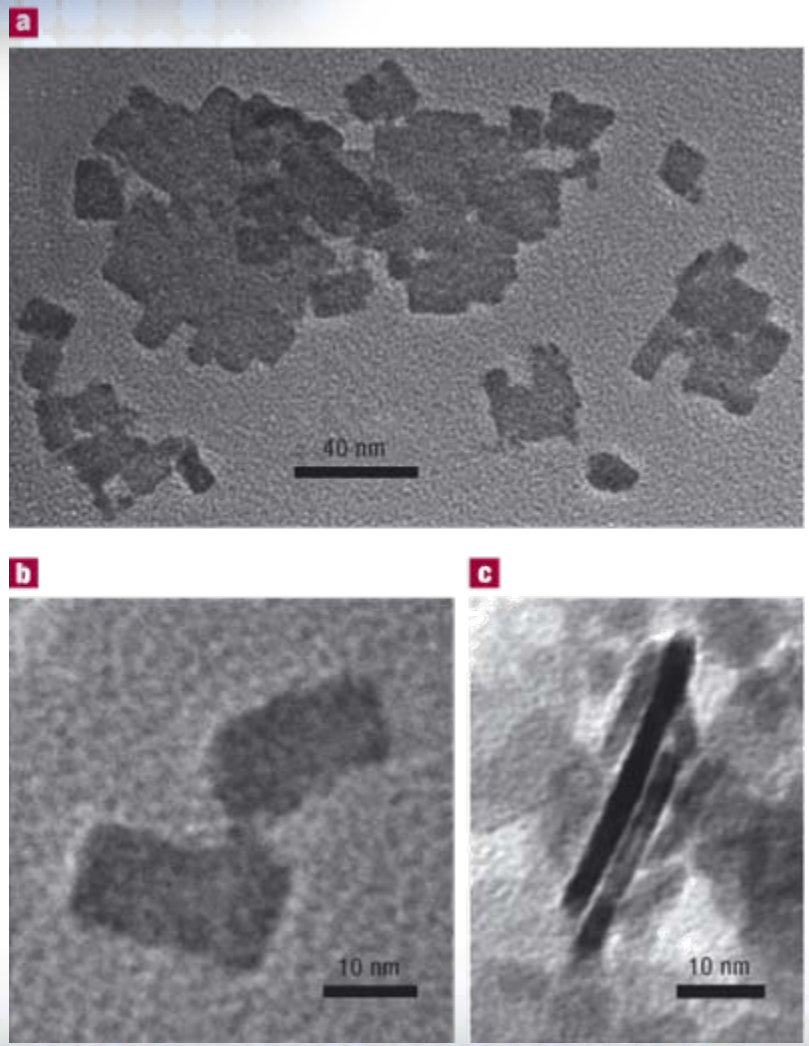
Extravasation Observed by Fluorescence



QDs coated with DHLA only- no fluorescence observed in interstitial fluid surrounding incision

QDs coated with DHLA-PEG ligand fluorescence observed from extravasated QDs

X-Ray Computed Tomography (CT) Imaging Agent Based on Bismuth Sulfide PVP Nanoparticles (BPNPs)



Polymer coated (PVP) NP prepared as an injectable CT imaging agent

Excellent stability

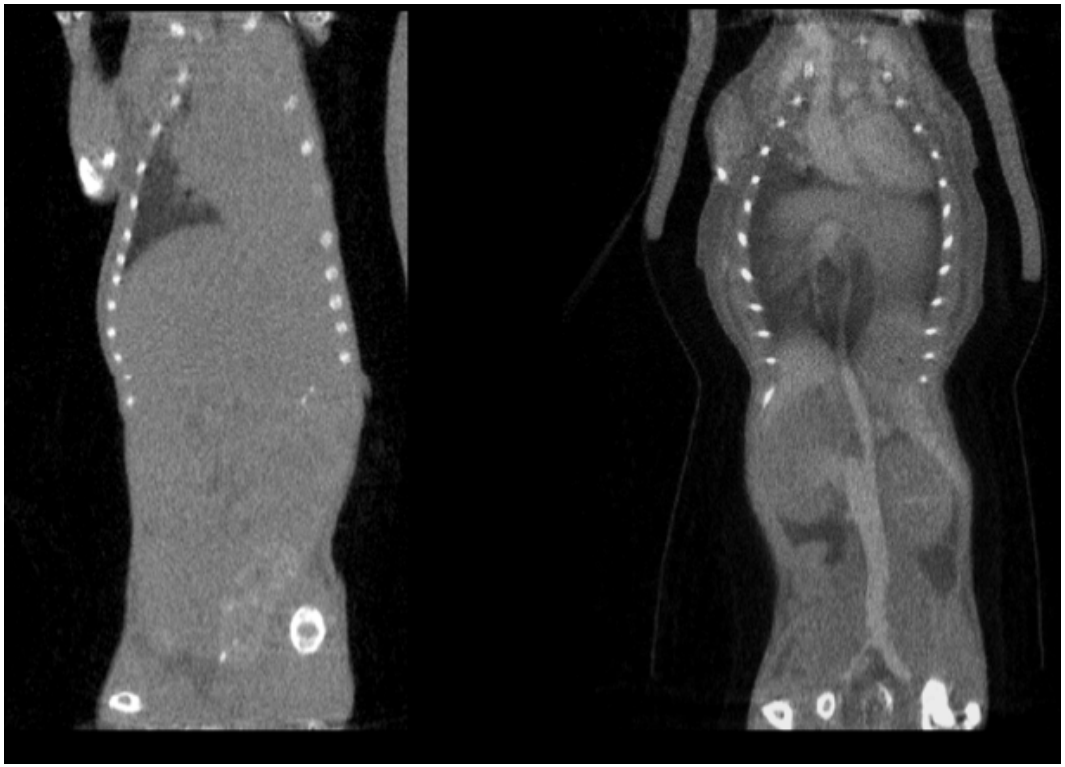
High x-ray absorption

Very long circulating times (>2 h in vivo)

Safety/efficacy better than current iodinated imaging agents

3-4 nm crystal thickness

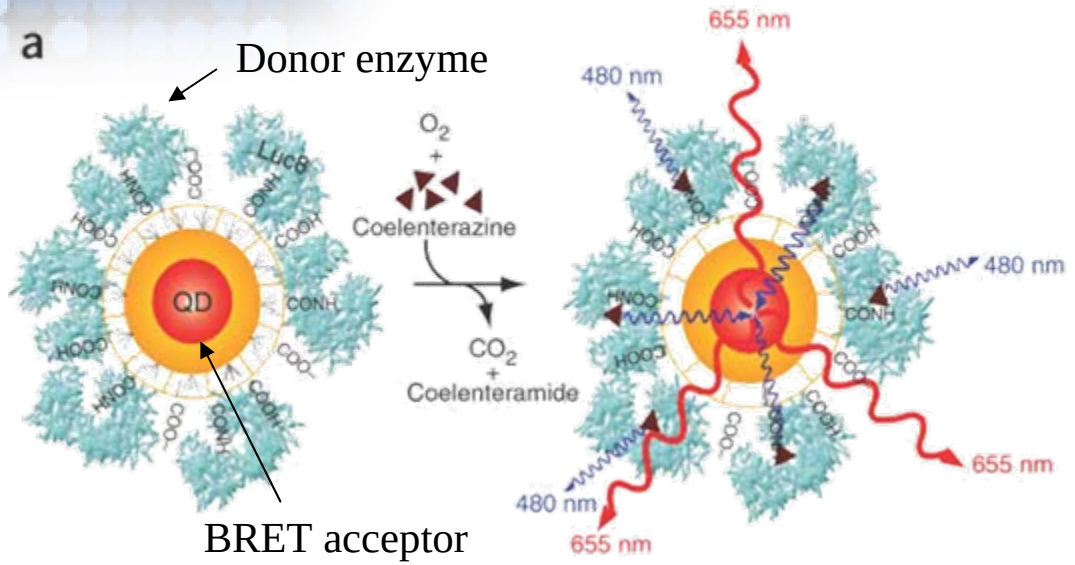
BPNPs Demonstrate Vascular Enhancement of Lungs and Heart and Organ Delineation

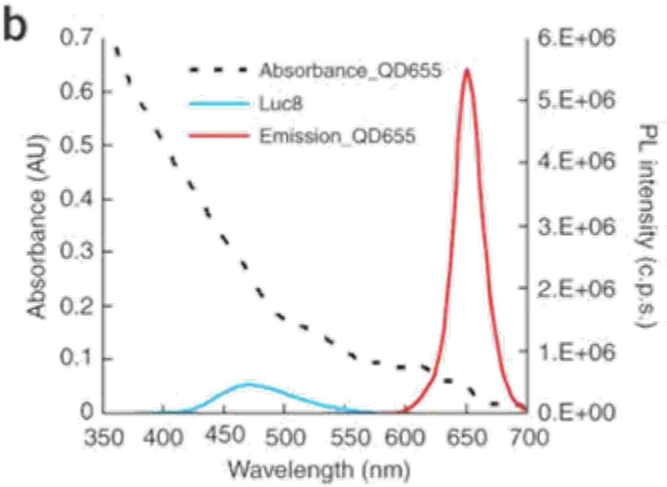


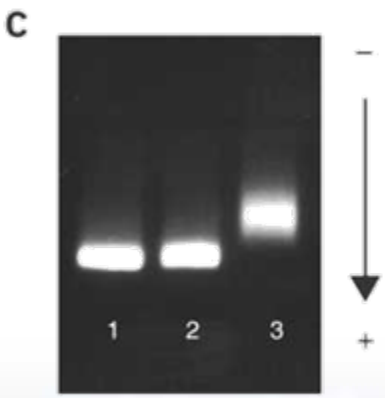
Before After

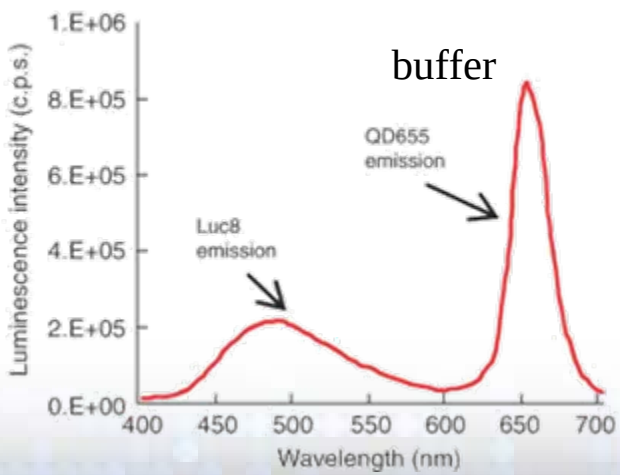
Image courtesy of Ralph Weissleder, M.D., Massachusetts General Hospital and Harvard Medical School
O. Rabin, et al., *Nature Materials*, 2006.

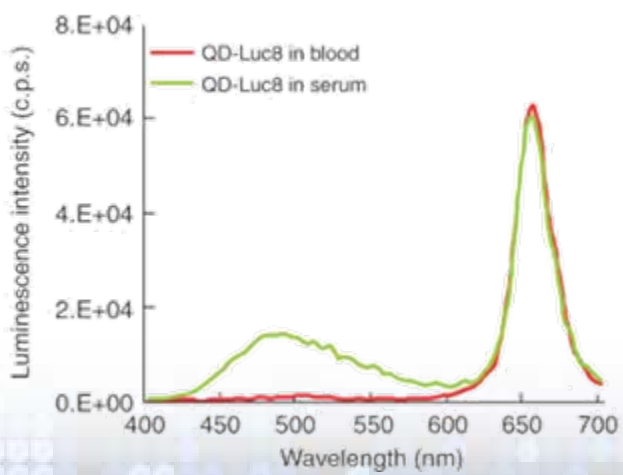
Self-illuminating Quantum Dot Conjugates Using Bioluminscence Resonance Energy Transfer (BRET)











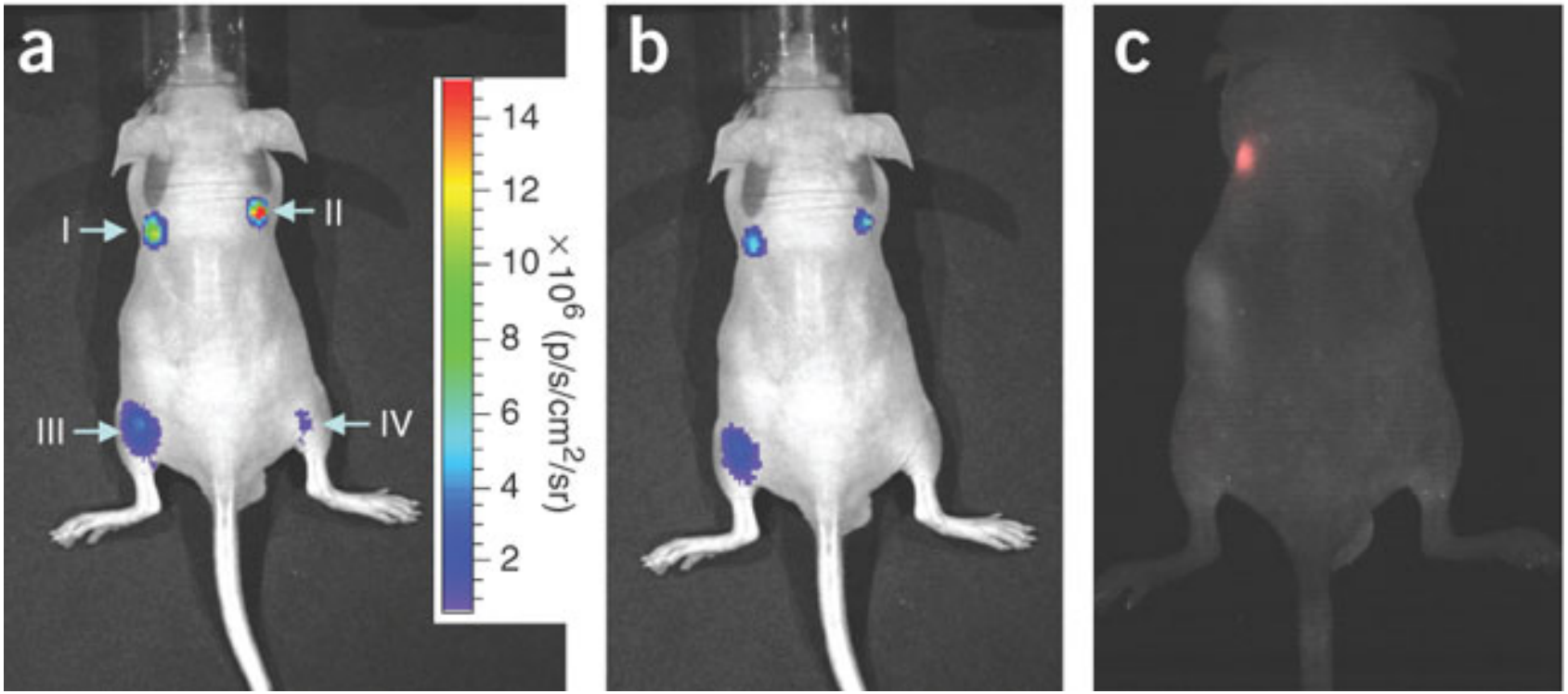
So et. al., Nature Biotechnology, Volume 24, Number 3, March 2006.

Biolumiscence and Fluorescence Imaging of QD-655 (CdSe/ZnS) and Luc8

No filter

575-650 filter

fluorescence

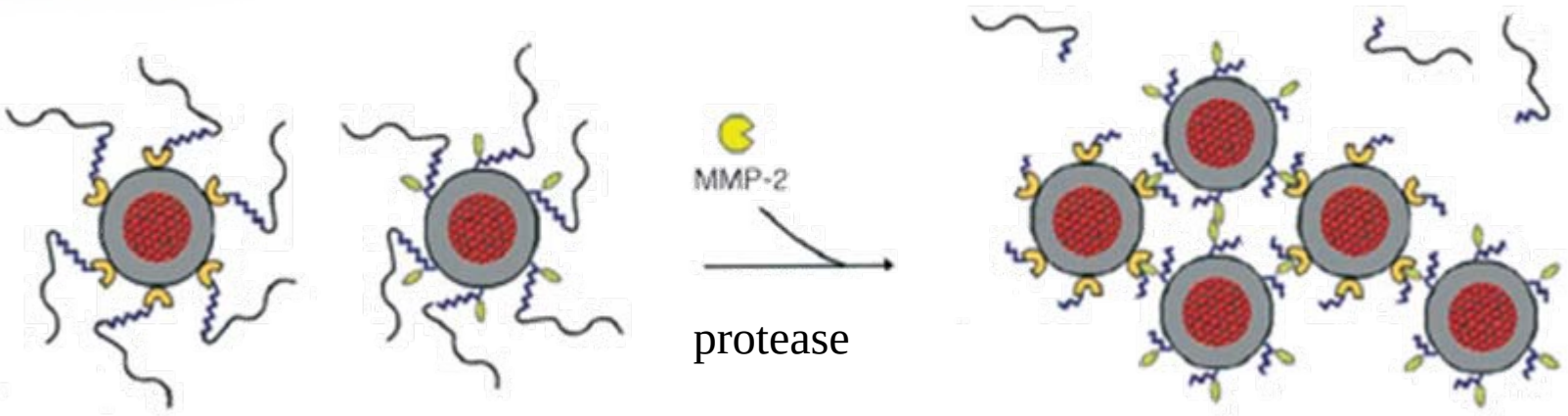


I and II are subcutaneous injections and III and IV are IM;
I and III are conjugate and II and IV are Luc8

Summary

- QD conjugates emit long-wavelength (red to NIR) bioluminescent light in cells and animals and in deep tissues
- Suitable for multiplexed *in vivo* imaging
- Self-illuminating QDs have greatly enhanced sensitivity in small animal imaging relative to existing QDs
- In vivo S/N of $>10^3$ for 5 pmol of conjugate

MRI Detection of Tumor Derived Cells via Proteolytic Actuation of Nanoparticle Assembly



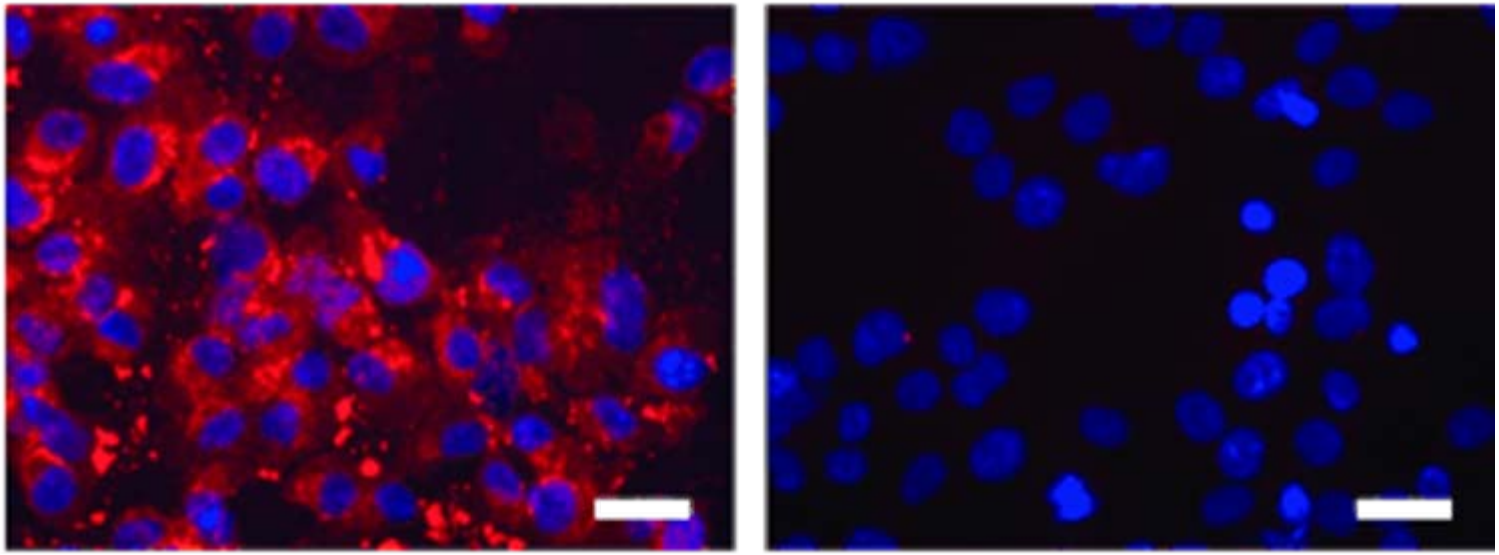
biotin and neutravidin coated Fe_3O_4 NPs with PEG

Nanoassemblies with:

- ↑ Magnetic susceptibility
- ↓ T2 relaxivity
- ↓ Diffusivity

Harris, Bhatia et al. Angew. Chem. Int. Ed. 2006, 45, 3161-3165

Assembly of Nanomaterials with Amplified Properties via Interaction with Processes of Disease

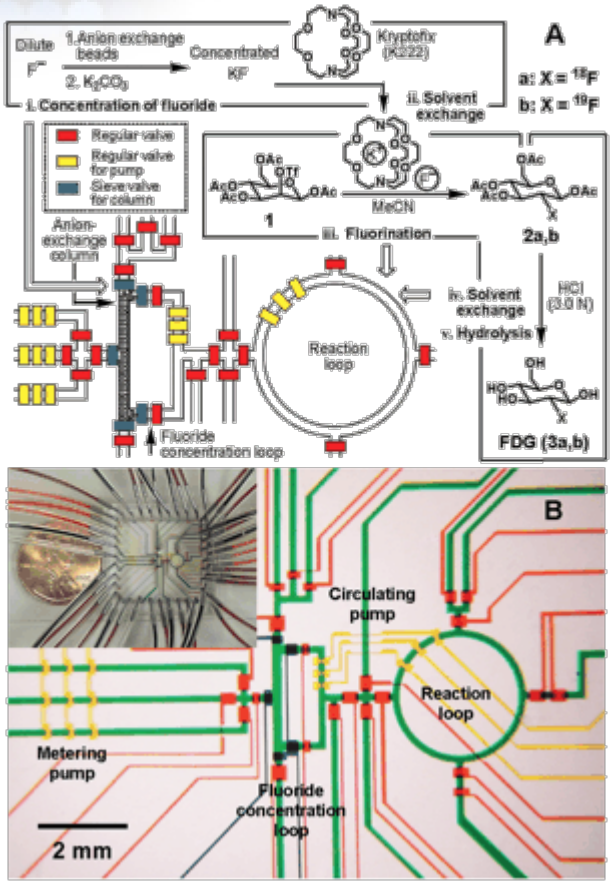


HT-1080/ No Inhibitor

HT-1080/ Inhibitor

Nanoparticle assembly amplifies T2 relaxation over cancer cells (secrete active MMP-2) relative to cells incubated with MMP inhibitor Galardin

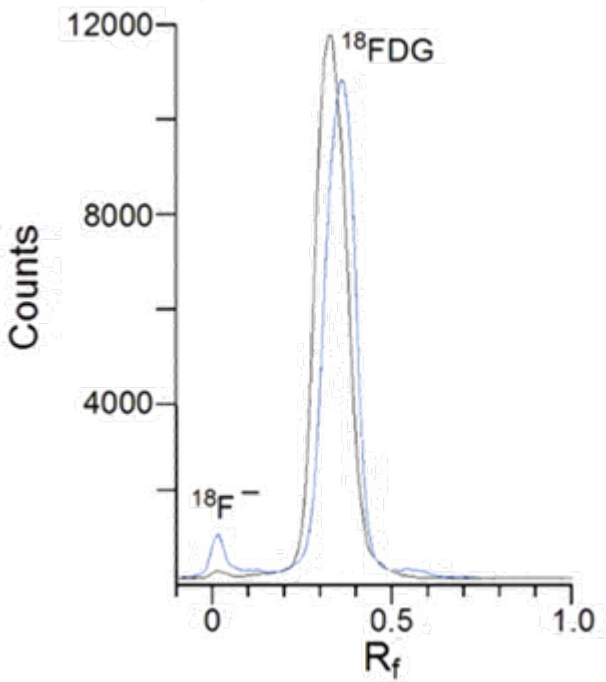
Multistep Synthesis of a Radiolabeled Imaging Probe Using Integrated Microfluidics



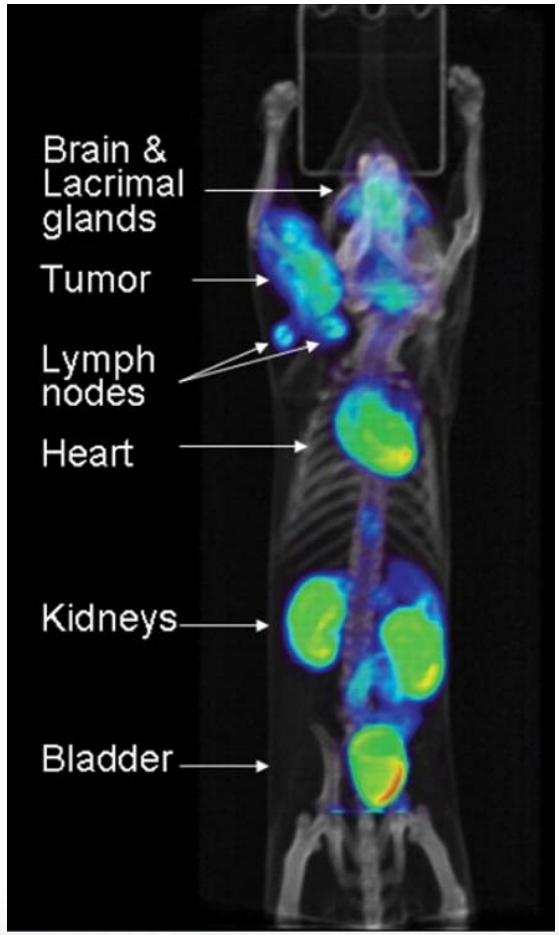
Five-step production of [18F] FDG PET molecular imaging probe in a nanoliter-scale reaction vessel

Tseng, et al. Science, Vol. 310, 16 December 2005.

MicroPET/MicroCT Image of Tumor-Bearing Mouse Injected with [18F] FDG Prepared on a Microfluidic Chip



TLC profile of unpurified and purified (99.3% radiochemical purity) and sterilized [18F] FDG



What Can Be Achieved

NCI's Technology-driven Initiatives:

- Foster new models for funding and conducting research
- Place a premium on collaboration and networking among multiple disciplines, multiple institutions
- Reshape the academic, government and private sector partnership
- Drive to milestones and deliverables for accountability

Provide the pathway to revolutionize the way we detect, treat and prevent cancer

The Future

New Generation of Diagnostics and Therapeutics

Biospecimens

Future Directions

- Technology Development
  - Caged pharmaceutical + some signal generator
    (material self-emits a signal in response to a delivery or drug effect)
  - Systems designed to give more dynamic rather than static data
  - Achieving good signal to noise for platforms which can sense hundreds or thousand of biomolecules

- Clinical Translation
  - Multifunctional nanoparticles (targeting, imaging, sensing, therapy)
  - Clinical trial design that couples endpoints for targeting and drug response

Recent Advances and Future Directions in Cancer Nanotechnology

CNST Nanotechnology Workshop
May 4, 2006
Urbana, Illinois

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